# Tandem Transplantation for Follicular Lymphoma: The Best of Both Worlds?

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Follicular lymphoma (FL) is the second most common type of non-Hodgkin's lymphoma with an incidence of ~15,000 new cases/year in the United States. The definite management of patients with FL remains under considerable debate due to the numerous treatment options available today. Such options include observation, chemotherapy, external beam radiation therapy, monoclonal antibodies, and radioimmunoconjugates [1]. Hematopoietic cell transplant (HCT) historically has been offered to younger patients and/or patients with fairly advanced disease. Autologous HCT (autoHCT) has unequivocally shown improved disease-free survival in patients with relapsed chemosensitive disease with 1 trial showing an overall survival benefit [2,3]. For patients with FL with relapsed disease, retrospective analyses have shown that autoHCT can provide benefit for patients who are not heavily pretreated before autoHCT [4]. There is no role for autoHCT as consolidation therapy in first remission as 3 randomized trials failed to demonstrate a survival advantage for autoHCT compared to conventional therapy [5-7].

Allogeneic HCT (alloHCT) represents the only treatment modality with curative potential for patient with FL. In contrast to autoHCT, alloHCT utilizes the graft vs lymphoma effect mediated by donor T cells and an allograft ameliorates the tumor cell contamination potentially associated with an autograft. There have been no completed randomized trials prospectively comparing autoHCT to alloHCT. A large, multicenter trial attempted to address this specific question but closed early due to poor accrual [8]. However, both retrospective and prospective alloHCT trials have consistently shown notably less relapse rates compared to autoHCT [9-12]. Due to the prohibitive nonrelapse mortality (NRM) associated with myeloablative conditioning regimens, reduced intensity conditioning (RIC) regimens have been increasingly offered with the goal of reducing NRM while utilizing the graft vs lymphoma effect as a form of adoptive immunotherapy. Several studies utilizing various RIC regimens have reported promising results with event free survival and overall survival (OS) ranging from 65% to 72% and 73% to 78%, respectively, with follow-up durations ranging from 3 to 9 years [10-12].

In this issue of *Biology of Blood and Marrow Transplantation*, investigators from the University of Montreal report the results of 27 patients with relapsed FL who received tandem autoHCT followed by RIC alloHCT using matched sibling donors [13]. The authors hypothesized that the high-dose chemotherapy with autoHCT would confer intense cytoreduction without the toxicity inherent with myeloablative alloHCT. Patients would then achieve a minimal disease state before proceeding to RIC alloHCT that aimed to eradicate minimal residual disease via adoptive immunotherapy. The majority of patients had chemosensitive disease but 19% were classified as chemorefractory. Five patients had evidence of transformed lymphoma and 7 patients were rituximab-naïve. Despite these unfavorable characteristics, the outcomes reported were impressive as the 3 year progression-free survival and OS were 96%. The median follow-up was 39 months. The NRM incidence was only 4% (1 patient died from graft-versus-host disease-related complications) and no graft failures were seen.

The concept of tandem auto/allo HCT is not a novel concept as this modality has been utilized in other lymphoma histologies and in multiple myeloma. However, the tandem HCT trial in this issue is the first report using tandem auto/alloHCT in patients with FL. The progression-free survival and OS of 96% is remarkable despite the fact that nearly 20% of patients were chemorefractory. Chemosensitivity at the time of alloHCT in patients with FL has been determined to be the most powerful prognostic factor for survival after alloHCT regardless of whether a myeloablative or RIC regimen was administered [14]. These results beg the question as to whether the intensive cytoreduction conferred by the autoHCT may have facilitated the graft-versus-lymphoma effect induced by the RIC alloHCT.

The notable results from this trial should be tempered by specific issues raised by the investigators, that the study design allowed patients to enroll and receive RIC alloHCT after autoHCT, which introduced selection bias.

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Tandem auto/alloHCT can now be added to the expansive list of treatment options for patients with relapsed FL. AlloHCT remains the only known cure for relapsed FL. However, tandem auto/alloHCT also carries obvious limitations as opposed to a single HCT which include the considerable cost of a double HCT and practical issues such as the lengthy time duration that the patient and his/her caregiver must allot for treatment and recovery time.

There is no consensus regarding the optimal timing of either autoHCT or alloHCT for patients with relapsed FL. Treatment choices must be individualized based on factors such as comorbidities, age, performance status, donor availability, and psychosocial issues.

In summary, tandem auto/alloHCT for FL may indeed offer the best of both worlds. Can an autoHCT considerably augment the effects of RIC alloHCT and thus overcome the negative prognostic outcome associated with chemorefractory disease? This question cannot be definitely answered based on a single published series but may open the door for a larger, confirmatory study especially for patients with chemorefractory disease.

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